Primary hypothyroidism and thyroid goiter in an adult cat

Galgano, M ; Spalla, I ; Callegari, C ; Patruno, M ; Auriemma, E ; Zanna, G ; Ferro, S ; Zini, E

DOI: https://doi.org/10.1111/jvim.12283

PRIMARY HYPOTHYROIDISM AND THYROID GOITER IN AN ADULT CAT

M. Galgano, I. Spalla, C. Callegari, M. Patruno, PhD, E. Auriemma, Dipl. ECVDI, G. Zanna, PhD, Dipl. ECVD, S. Ferro, and E. Zini, PD, PhD, Dipl. ECVIM

From the Istituto Veterinario di Novara, Italy (Galgano, Callegari, Auriemma, Zanna, Zini); the Clinica Veterinaria I Ronchi, Gallarate, Varese, Italy (Spalla), the Department of Comparative Biomedicine and Food Science, Veterinary Medicine, University of Padova, Italy (Patruno, Ferro); the Studio Dermatologico Veterinario, Italy (Zanna); the Clinic for Small Animal Internal Medicine, University of Zurich, Switzerland, and the Department of Animal Medicine, Production and Health, University of Padova, Italy (Zini).

Corresponding author: Eric Zini, PD, PhD, Dipl. ECVIM, Clinic for Small Animal Internal Medicine, University of Zurich, 8057 Zurich, Switzerland; e-mail: ezini@vetclinics.uzh.ch

A 5-year old, neutered male domestic shorthair cat was referred for evaluation of suspected hypothyroidism. In the previous 2 months the owner reported mild lethargy, weight gain and reduced appetite, unkempt hair coat and an episode of bilateral external otitis that temporarily improved completing a 10 days treatment with ear drops containing gentamicin, betamethasone and clotrimazole[a]; treatment was terminated 50 days before. The cat was slightly overweight since several months before consulting with the veterinarian, but more precise information was not available from the owner. The cat was started on a commercial diet to control obesity[b]. One month prior to admission the referring veterinarian performed a complete blood count, a serum biochemical profile and urinalysis that were unremarkable. In addition, serum total thyroxine (TT4) was within normal limits (1.1 µg/dL; reference range, 0.8-4.7) and free thyroxine (fT4), measured by chemiluminescence immunoassay (CLIA), was low (< 3.9 µg/dL; reference range, 9.0-33.5).

On admission the cat was obese (body condition score, 8/9[c]) with a body weight of 7.6 kg, and had unkempt hair coat with diffuse scaling and ventral hypotrichosis (Fig. 1). On palpation of the thyroid region, bilateral symmetrical nodules with a diameter of approximately 2-3 cm each were detected. Based on a dermatological examination, widespread exfoliative dermatosis and bilateral ceruminous otitis externa were diagnosed. Fungal culture of plucked hairs and scraped scales yielded *Microsporum canis* infection.

The thyroid panel was repeated at the same laboratory and revealed a low TT4 (< 0.7 µg/dL; reference range, 0.8-4.7), a low fT4 measured at equilibrium dialysis (< 0.4 ng/dL; reference range, 0.7-2.3), and a high canine thyroid-stimulation hormone (TSH) concentration (5.6 ng/mL; reference range, < 0.5), leading to a diagnosis of primary hypothyroidism. The cat was started on oral levothyroxine[d] at the dosage of 0.1 mg, once daily. In addition, topic econazole, twice a

week, and oral itraconazole, once daily at the dosage of 5 mg/kg, were prescribed for the dermatophytosis.

To investigate the thyroid gland and identify any ectopic thyroid tissue, and to characterize the pituitary gland, a computed tomography (CT) of the head, neck and chest were scheduled 5 days later under general anesthesia, along with surgical excision of a thyroid nodule. Before induction of anesthesia an electrocardiogram and echocardiography were performed that revealed no abnormality. The CT was obtained with helical acquisition using a 4 slices scanner[e] with 1.25 mm slices thickness (acquisition parameters: 120 kV, 160 mAs, 1 pitch). After intravenous administration of 2 ml/kg iohexol[f] a dynamic study of the pituitary gland was obtained continuously scanning in sequence from the rostral to the caudal margin of the *sella turcica* until washing-out of the contrast medium[1]. Thereafter, a second dose of iohexol was given (1 ml/kg) and contrast medium enhanced images of the thyroid were acquired. The CT showed two symmetric masses originating from the thyroid lobes connected by a thin isthmus (left lobe, size: 0.8 x 1.2 x 3.2 cm; right lobe, size: 0.6 x 1.0 x 2.3 cm) (Fig. 2). The thyroid tissue was isoattenuating to the surrounding musculature (average pre-contrast Hounsfield Units 41.7). The pituitary gland, brain, and thorax were unremarkable.

An excisional biopsy of the right lobe of the thyroid gland, which grossly appeared dark red, was fixed in 10% neutral buffered formalin and embedded in paraffin; 4 μm cuts were obtained and stained with hematoxylin and eosin, and periodic acid-Shiff (PAS). At light microscopy, the thyroid parenchyma was characterized by large lobules containing follicles (Fig. 3). Follicles were variable in size, often very small, irregularly shaped or collapsed multifocally, and lined by one or more layers of follicular cells. The follicular lumina were generally empty, occasionally filled with scant amorphous homogenous PAS-positive material, consistent with colloid. Some

colloid vacuoles were evident. Follicular cells were increased in number and size. Cells were cuboidal with moderate, non-homogenous, slightly eosinophilic, sometimes vacuolated cytoplasm, and had round, centrally located nucleus with finely granular to marginated chromatin and one small nucleolus. Anisocytosis and anisokaryosis were mild. Mitoses were absent. Finally, occasional mildly extended hemorrhages were evident throughout the tissue. These findings were consistent with diffuse follicular hyperplasia of the thyroid gland. From the same thyroid sample an aliquot was prepared for transmission electron microscopy. The tissue was reduced to small segments of 1 mm in length, further fixed with 2% glutaraldehyde in 0.1 M cacodylate buffer, pH 7.4, and processed for analysis. Sections were stained with uranyl acetate and lead citrate and were examined with a dedicated microscope[g]. The rough endoplasmatic reticulum (RER) of most thyroid cells was severely dilated, with distended cisternae. Mitochondria were sparse, reduced in numbers, sometimes slightly swollen. Lysosomes, exocytic and endocytic vesicles were few and scattered, and nuclei were centrally displaced or in some cells apically displaced (Fig. 4).

One month later, because the cat was still mildly lethargic and presented diffuse scaling of the epidermis, and had no improvement in serum fT4 (< 0.4 ng/dL) and TSH (9.8 ng/mL), levothyroxine was increased to 0.4 mg, once daily. After 4 additional weeks the owner reported that the cats was again bright and alert whereas skin lesions were not ameliorated; fT4 was measure and resulted above the upper limit of the reference range (4.6 ng/dL) and levothyroxine was thus lowered to 0.2 mg. Following another month the cat was still bright and alert, skin lesions had improved (Fig. 5) and antifungal treatment was discontinued: a month later, fT4 was normal (1.1 ng/dL) but TSH remained elevated (> 12 ng/mL). At the time of writing, 8 months

following diagnosis, the cat is still in good health, without skin lesions but with palpable goiter; the cat continues on levothyroxine at 0.2 mg.

In cats the most common form of hypothyroidism is iatrogenic, due to bilateral thyroidectomy[2], radioactive iodine treatment[3] or overdose of anti-thyroidal drugs[4]. Recently, a case of secondary hypothyroidism following head trauma has been reported in an 18 month old cat[5]. Spontaneous feline hypothyroidism is a rare condition, more common in kittens than in adults. In the former, all cases described were congenital, presumably with a genetic basis leading to either dyshormonogenesis (goiterous) or dysmorphogenesis (nongoiterous)[6,7,8,9]. Congenital hypothyroidism is characterized by dwarfism. The first signs of abnormal growth become evident already after 3 weeks and are most evident by 2 months of age. Kittens may also show hypotonia, macroglossia, distended abdomen, dry skin, delayed dental eruption, and central or peripheral nervous system abnormalities[10].

Spontaneous adult-onset hypothyroidism is extremely rare in cats, with only two documented cases[11,12]; based on histopathology in one cat it was secondary to lymphocytic thyroiditis and in the other no identifiable thyroid tissue was found. The most common clinical signs of hypothyroidism in adult cats include lethargy, hypothermia and obesity. Reduced appetite and weight gain, despite prescription of a caloric restricted diet, has been reported. Dermatological abnormalities, including focal alopecia, hyperpigmentation, seborrhea and pyoderma, demodicosis or dermatophytosis secondary to reduced cutaneous immunity, and myxedema have been described[10]. Similar to previous reports, the present cat was mildly lethargic, and was obese with reduced appetite. The dermatological abnormalities of the cat were also characteristic for hypothyroidism.

With regard to hematological analyses, adult-onset hypothyroid cats are usually unremarkable; one cat had elevated serum concentrations of creatine-kinase[5,11]. The mechanism for the increased creatine-kinase in cats may be due to hypothyroid myopathy, as has been reported in dogs[10]. The present cat had unremarkable blood tests, including serum creatine-kinase, and urinalysis.

Diagnosing hypothyroidism in adult cats has been made via a combination of basal serum TT4, fT4 and endogenous TSH. As in hypothyroid dogs, affected cats are expected to have low serum TT4 and fT4 concentrations and a high TSH concentration. With regard to the latter, the canine TSH enzyme-linked immune-sorbent assay (ELISA) has been used to detect feline TSH[14]; the assay may be helpful to detect cases of iatrogenic hypothyroidism although it has never been tested in cases of spontaneous hypothyroidism. Cats with primary hypothyroidism, either iatrogenic or spontaneous, are expected to have elevated concentrations of TSH and those with secondary hypothyroidism to have decreased concentrations[5,14]. In the cat of this report, low TT4 and fT4 concentrations were documented along with elevated TSH, leading to a diagnosis of primary hypothyroidism. Of note, in geriatric cats, low or low-normal TT4 concentrations are often caused by non-thyroidal illness (euthyroid sick syndrome) or can occur following administration of drugs such as corticosteroids and barbiturates. Because fT4 measured at equilibrium dialysis may have limited specificity in cats, in this species its use in clinical practice should be combined with measurement of TT4 concentrations[15]. Of note, along with decreased TT4 and fT4, the increased TSH documented in the present case should make the hypothesis of sick euthyroid syndrome very improbable.

Our cat had received eardrops containing betamethasone but long before presentation and fT4 was decreased, making the effect of corticosteroids on thyroid hormones unlikely. The

128 dermatological disorder of the cat was secondary to hypothyroidism as shown by its full recovery
129 following replacement therapy.
130 With regard to diagnostic imaging, in humans the normal thyroid is hyperattenuating to the
131 surrounding tissues in CTs acquired without contrast medium[16]. The high attenuation is directly
132 related to thyroid iodine content. Hypothyroidism leads to isoattenuating or hypoattenuating
133 glands compared to adjacent muscle in humans[17]. This occurs if the thyroid contains less iodine,
134 and if more follicular cells or interstitial tissue is present. The normal feline thyroid gland is
135 hyperattenuating to surrounding tissues without contrast medium[16]. In our cat the thyroid tissue
136 was isoattenuating as shown in hypothyroid people, possibly due to less iodine content or to
137 diffuse follicular hyperplasia. In addition, brain and thorax scans were normal, excluding
138 pituitary lesions and ectopic thyroid tissue.
139 The present cat had a palpable thyroid gland. Unilateral or bilateral lobe enlargement is
140 detectable in cats with thyroid nodules, as it often happens in hyperthyroidism, and was palpable
141 in several cats with congenital hypothyroidism[6,12] but has never been recognized in cats with
142 adult-onset hypothyroidism. Goiter refers to an enlarged thyroid gland; in mammals goiter is
143 associated either with euthyroidism, hypothyroidism or hyperthyroidism. Goitrogenic
144 mechanisms associated with hypothyroidism include iodine dietary deficiency or excess,
145 ingestion of goitrogenic compounds, and genetic defects[18]. These causes lead to inadequate
146 thyroxine synthesis or secretion and low thyroid hormone concentrations, causing a
147 compensatory increase of TSH. In turn, long-term elevated TSH results in hypertrophic and
148 hyperplastic follicular cells; lobes are enlarged and dark-red for the presence of an extensive
149 parenchymal capillary network, as was for the present cat. Microscopically there are two
150 patterns, the diffuse hyperplastic goiter and the colloid goiter. The first is characterized by

diffuse follicular cells hyperplasia, with one or more layer of tall, columnar cells, and irregularly sized and shaped, or collapsed follicles[18,19]; colloid in the lumina is usually scarce or absent. These features were similar to our cat. Colloid goiter is the involutionary phase of diffuse hyperplastic goiter, it occurs when thyroid hormone request is diminished or a sufficient amount of iodine is added to the diet. After increase of blood thyroid hormone concentrations, the TSH diminishes, and the hyperplastic follicular cells continue to produce colloid, but the endocytosis of colloid from the lumen is decreased. As a consequence, the follicles are distended by large amount of colloid and the epithelium is flattened[18,19]. With regard to transmission electron microscopic analysis, major lesions were observed in the RER of the present cat, which was severely dilated. RER dilation is a non thyroid specific degenerative change, secondary to different cellular stressors or sublethal injuries; its presence does not differentiate between congenital or acquired disease. Swollen mitochondria and decreased number of mitochondria, scattered lysosomes and vescicles, as in the present cat, can also be observed in both forms. Although these lesions have not been previously described in cats, they have been documented in rats, mice and humans affected by congenital and acquired thyroid dysfunction[20,21,22].

In humans and animals, goitrogenic compounds are represented by drugs and synthetic or natural chemicals as sulfonamides, benzodiazepines, plants of the genus Brassica, and other xenobiotics[18]. Our cat lived indoor in a large multiple cat household and was the only one showing clinical signs of hypothyroidism. Therefore, the chance of exposure to goitrogenic compounds seems very low, even though blood analyses were not performed in the remaining cats to exclude further cases of hypothyroidism. In humans, besides goitrogenic substances, acquired adult-onset primary hypothyroidism with goiter may be secondary to iodine deficiency[23] or, although less commonly, iodine excess[24]. Whether the cat had iodine dietary

imbalance cannot be excluded. Indeed, all cats were fed the same food except the present one, which was fed a caloric restricted diet. However, based on listed ingredients, the new diet contains adequate amount of iodine (2.5 mg iodine/kg of dry diet), fulfilling to recent feline nutritional recommendations[25]. Thus, the role of the new diet in the development of hypothyroidism seems less plausible. Of note, it cannot be excluded that the cat was chronically exposed to low doses of thyrotoxic substances, leading to hypothyroidism and in turn causing progressive increase of TSH concentrations, as documented during follow-up. However, it seems difficult to support this hypothesis since in the large multiple cat household he was the only one with overt hypothyroidism. Increased TSH concentrations, despite replacement therapy, has been shown in a Toy Fox Terrier with congenital goiter[26]. As assumed in that dog, it is possible that the dose or frequency of thyroxine given to the present cat was not enough to decrease TSH. Alternatively, it cannot be excluded that absorption of thyroxine from the gastrointestinal tract decreased over time or that peripheral tissue resistance to thyroid hormone developed. However, the pathogenesis of increased TSH in the cat remains unclear, especially considering the significant clinical improvement. .

Hypothyroidism and goiter are observed with different inborn errors of the thyroid hormone biosynthetic pathway (dyshormonogenesis[18,22,27]). In our cat, a congenital form may appear less likely because clinical signs developed in adulthood and dwarfism, which has been identified in all feline congenital cases, was not present. Of note, however, in humans there are forms of congenital hypothyroidism that can remain subclinical for a long period. An increase of TSH secretion is able to maintain TT4 within normal limits and only few develop clinically overt hypothyroidism during childhood or later. Hence, it cannot be excluded that the present cat had a subclinical congenital form of hypothyroidism that became clinically evident only during

adulthood. Persistence of a palpable goiter during treatment, despite adequate response to supplementation, might also indicate a subclinical congenital defect.

In conclusion, a cat affected by adult-onset primary hypothyroidism and goiter is presented, where a dietary iodine imbalance or low-chronic exposure to thyrotoxic substances, and a congenital form with late clinical development may have played a causative role.

Footnotes

[a] Surolan, Merial, Milano, Italy

[b] Obesity Management (Feline), dry, Royal Canin, Milano, Italy

[c] Nine-point body condition scale for cats, Nestlé Purina, St. Louis, MI

[d] Leventa, Intervet Italia Spa, Milano, Italy

[e] Light Speed; GE Medical System, Bergamo, Italy

[f] Visipaque, 305mgI/ml, Nycomed Inc., Princeton, NJ

[g] Philips CM10 TEM, Eindhoven, Germany

Abbreviations:

CLIA, chemiluminescence immunoassay; CT, computed tomography; fT4, free thyroxine; PAS, periodic acid-Shiff ; RER, rough endoplasmatic reticulum; TT4, serum total; TSH, Thyroid-stimulating hormone.

Reference

1. Van der Vlugt-Meijer RH, Meij BP, Voorhout G. Dynamic helical computed tomography of the pituitary gland in healthy dogs. Vet Radiol Ultrasound 2007;48(2):118-124
2. Birchard SJ. Thyroidectomy in the cat. Clin Tech Small Anim Pract 2006;21(1):29-33
3. Peterson ME. Radioiodine treatment of hyperthyroidism. Clin Tech Small Anim Pract 2006;21(1):34-39
4. Williams TL, Elliott J, Syme HM. Association of iatrogenic hypothyroidism with Azotemia and reduced survival time in cats treated for hyperthyroidism. J Vet Intern Med 2010; 24(5):1086-1092
5. Mellanby RJ, Jeffery ND, Gopal MS, Herrtage ME. Secondary hypothyroidism following head trauma in a cat. J Feline Med Surg 2005;7(2):135-139
6. Jones BR, Gruffydd-Jones TJ, Sparkes AH, Lucke VM. Preliminary studies on congenital hypothyroidism in a family of abyssinian cats. Vet Rec 1992;131(7):145-148
7. Crowe A. Congenital hypothyroidism in a cat. Can Vet J 2004;45(2):168-170
8. Traas AM, Abbott BL, French A, and Giger U. Congenital thyroid hypoplasia and seizures in 2 littermate kittens. J Vet Intern Med 2008;22(6):1427-1431
9. Quante S, Fracassi F, Gorgas D et al. Congenital hypotyroidism in a kitten resulting in decreased IGF-I concentration and abnormal liver function test. J Feline Med Surg 2010;12(6):487-490
10. Greco DS. Diagnosis of congenital and adult-onset hypothyroidism in cats. Clin Tech Small Anim Pract 2006;21(1):40-44
11. Rand JS, Levine J, Best SJ, Parker W. Spontaneous adult-onset hypothyroidism in a cat. J Vet Intern Med 1993;7(5):272-276

12. Blois SL, Abrams-Ogg ACG, Mitchell C et al. Use of thyroid scintigraphy and pituitary immunohistochemistry in the diagnosis of spontaneous hypothyroidism in a mature cat. J Feline Med Surg 2010;12(2):156-160
13. Reusch CE, Gerber B, Boretti FS. Serum fructosamine concentrations in dogs with hypothyroidism. Vet Res Commun 2002;26(7):531-6
14. Graham PA, Refsal KR, Nachreiner RF et al. Measurement of feline thyrotropin (TSH) using a commercial canine immunoradiometric assay. J Vet Intern Med 2000;14:342.
15. Mooney CT, Little CJ, Macrae AW. Effect of illness not associated with the thyroid gland on serum total and free thyroixine concentrations in cats. J Am Vet Med Assoc 1996;15;208(12):2004-2008
16. Drost WT, Mattoon JS, Samii VF et al. Computed tomographic densitometry of normal feline thyroid glands. Vet Radiol Ultrasound 2004;45(2):112-116
17. Silverman PM, Newman GE, Korobkin M et al. Computed tomography in the evaluation of thyroid disease. Am J Roentgenol 1984;142(5):897-902
18. Jubb, Kennedy, Palmer's pathology of domestic animals, 5th ed. Saunders Elsevier 2007;3:389-396
19. Kiupel M, Capen C, Miller M, Smedley R. Histological classification of tumors of the endocrine system of domestic animals, second series 2008;XII:33-35
20. Ketelbant-Balasse P, Glinoer D, Neve P. Ultrastructural aspects of the thyroid in a case of human congenital goitre with cretinism. Pathol Eur 1975;10(2):155-165
21. Krupp PP, Lee KP. The effects of dietary iodine on thyroid ultrastructure. Tissue Cell 1988;20(1):79-88

22. Medeiros-Neto G, Kim PS, Yoo SE et al. Congenital hypothyroid goiter with deficient thyroglobulin identification of an endoplasmic reticulum storage disease with induction of molecular chaperones. J Clin Invest 1996;15;98(12):2838–2844

23. Zimmermann MB. The role of iodine in human growth and development. Semin Cell Dev Biol 2011;22:645–652

24. Wolff J. Iodide goiter and the pharmacologic effects of excess iodide. Am J Med. 1969;47(1):101-124

25. Wedekind KJ, Blumer ME, Huntington CE et al. The feline iodine requirement is lower than the 2006 NRC recommended allowance. J Anim Physiol Anim Nutr (Berl) 2010;94(4):527–539

26. Fyfe JC, Kampschmidt K, Dang V et al. Congenital hypothyroidism with goiter in toy fox terriers. J Vet Intern Med 2003;17(1):50-57

27. Park SM, Chatterjee VKK. Genetics of congenital hypothyroidism J Med Genet 2005;42:379-389

Figure captions

Figure 1

Picture of the cat on admission; note the diffuse scaling with unkempt hair coat.

Figure 2

Transverse precontrast (A) and postcontrast (B) computed tomographic images of the neck. The thyroid tissue (arrows), is isoattenuating to the surrounding musculature in the precontrast image (A) and is hyperattenuating in the postcontrast image (B).

Figure 3

Thyroid, cat. At low magnification the architecture of the organ appears alterated: the lobules are densely cellular, with variably sized or collapsed follicles. The follicular lumen are smaller than normal, irregularly shaped and often empty. Bar = 200 μm, PAS stain. Left inset: high magnification of a follicle. Multiple small pseudo-vacuoles (asterisks) are visible in the lumen due to the intense endocytosis of colloid typical for diffuse hyperplasia. HE. Right inset: two adjacent follicles at high magnification. The follicle on the left contains a small amount of colloid, weakly stained with PAS (white asterisk) in contrast of the follicle on the right which has an empty lumen (black asterisk). PAS.

Figure 4

Transmission electron microscopic image of two follicular thyroid cells. The RER, predominantly at the base of the nucleus, is severely dilated, with distended cisternae.

299 Lysosomes and secretory vesicles are not evident. The follicular lumen, in the right upper part of
300 the image, is empty. Bar = 10 μm.
301
302 **Figure 5**
303 Picture of the cat 7 months after treatment; hair coat is improved and scaling is not present.